NEWS RELEASE

FDA Approves Merck's KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) Injection for Subcutaneous Use in Adults Across Most Solid Tumor Indications for KEYTRUDA® (pembrolizumab)

2025-09-19

KEYTRUDA QLEX is the first and only subcutaneously administered immune checkpoint inhibitor that can be given by a health care provider in as little as one minute

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) injection for subcutaneous administration in adults across most solid tumor indications for KEYTRUDA® (pembrolizumab). Berahyaluronidase alfa is a variant of human hyaluronidase developed and manufactured by Alteogen Inc. KEYTRUDA QLEX must be administered by a health care provider (HCP). Merck expects to have KEYTRUDA QLEX (pronounced key-TRUE-duh Q-lex) available in the U.S. in late September. For a full list of the 38 indications for which KEYTRUDA QLEX is approved, see "KEYTRUDA QLEX Indications" below.

"This approval is significant for patients and health care providers like me who have been using immunotherapies for years to treat certain cancers. We now have a new option with a broad set of indications that has demonstrated comparability with intravenous (IV) pembrolizumab but in a subcutaneous injection that can be administered in one minute every three weeks or two minutes every six weeks," said Dr. J. Thaddeus Beck, oncologist and Medical Director of the Highlands' Clinical Trials Office. "Subcutaneous pembrolizumab provides faster administration than

IV pembrolizumab, offers two dosing options and gives patients more choices of health care settings in which they can receive their therapy."

The pivotal trial comparing subcutaneous KEYTRUDA QLEX to IV KEYTRUDA administered every six weeks, each with chemotherapy, was conducted in patients with treatment-naïve metastatic non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 genomic tumor aberrations. This trial demonstrated comparable pharmacokinetic exposure levels to pembrolizumab [assessed as Cycle 1 AUC0-6 weeks (area under the curve from 0 to 6 weeks) and Cycle 3 (i.e. Steady State) Ctrough]. In descriptive efficacy analyses, overall response rates (ORR) were similar between KEYTRUDA QLEX and KEYTRUDA (45% [95% CI: 39, 52] vs 42% [95% CI: 33, 51]). Additionally, no notable differences were observed in progression-free survival (PFS) and overall survival (OS). Effectiveness of KEYTRUDA QLEX for its approved indications was established based on these data and pivotal trial data demonstrating comparable safety with KEYTRUDA, as well as evidence from adequate and well-controlled studies conducted with KEYTRUDA.

KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients. Additionally, immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection and other transplant (including corneal graft) rejection. Additionally, fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment. Consider the benefit versus risks for these patients. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials due to the potential for increased mortality. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA QLEX. Based on the severity of the adverse reaction, KEYTRUDA QLEX should be withheld or permanently discontinued and corticosteroids administered if appropriate. KEYTRUDA QLEX can also cause severe or life-threatening administration-related reactions. Based on its mechanism of action, KEYTRUDA QLEX can cause fetal harm when administered to a pregnant woman. For more information, see "Selected Important Safety Information" below.

As a subcutaneous injection, KEYTRUDA QLEX may provide added convenience compared to IV KEYTRUDA because it can be administered by HCPs in multiple settings from an infusion center to a doctor's office or a local community-based clinic, providing more options where patients can receive their treatment. KEYTRUDA QLEX also provides flexibility in treatment administration. It can be given in one minute every three weeks or in two minutes every six weeks, requiring substantially less time to administer than a 30-minute IV infusion of KEYTRUDA, and also

offers a choice of injection site in the thigh or abdomen avoiding the 5 cm area around the navel. For patients who do not require a port or whose veins are difficult to access, subcutaneous administration may simplify treatment administration.

“At Merck, we are committed to putting patients first, as we work relentlessly to discover new options that may help patients manage their treatment in a way that fits their needs,” said Dr. Marjorie Green, senior vice president and head of oncology, global clinical development, Merck Research Laboratories. “We are honored to build on the foundation of KEYTRUDA with KEYTRUDA QLEX, a new injectable immunotherapy option that has similar results to KEYTRUDA and can be administered in as little as one minute.”

“As part of supporting patients and families through their cancer journeys, we are excited to see patient-focused developments in subcutaneous cancer treatment that shorten administration time and may allow for more patients to receive treatment in multiple health care settings,” said Sally Werner, Chief Executive Officer, Cancer Support Community.

Study 3475A-D77 trial design and additional data supporting the approval

Study 3475A-D77 is a multicenter, randomized, open-label, active-controlled Phase 3 trial (ClinicalTrials.gov, **NCT05722015**) conducted in patients with treatment-naïve metastatic non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 genomic tumor aberrations. The primary outcome measure was pembrolizumab exposure [Cycle 1 AUC0-6 weeks and Cycle 3 (i.e. Steady State) Ctrough] of subcutaneous KEYTRUDA QLEX as compared to IV pembrolizumab. Additional descriptive efficacy outcome measures were ORR by blinded independent central review (BICR), PFS by BICR and OS.

A total of 377 patients were randomized 2:1 to receive either KEYTRUDA QLEX (790 mg/9,600 units) every six weeks with platinum doublet chemotherapy (n=251) or pembrolizumab (400 mg) every six weeks with platinum doublet chemotherapy (n=126).

At the primary analysis, the confirmed ORR was 45% (95% CI: 39, 52) in the subcutaneous KEYTRUDA QLEX arm versus 42% (95% CI: 33, 51) for IV pembrolizumab arm. There were no notable differences in PFS and OS observed in patients who received KEYTRUDA QLEX compared to patients who received IV pembrolizumab.

The most common adverse reactions (≥20%) of patients who received KEYTRUDA QLEX in combination with chemotherapy were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).

About KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) injection for subcutaneous use

KEYTRUDA QLEX is a fixed-combination drug product of pembrolizumab and berahyaluronidase alfa. Pembrolizumab is a programmed death receptor-1 (PD-1) blocking antibody and berahyaluronidase alfa enhances dispersion and permeability to enable subcutaneous administration of pembrolizumab. KEYTRUDA QLEX is administered as a subcutaneous injection into the thigh or abdomen, avoiding the 5 cm area around the navel, over one minute every three weeks (2.4 mL) or over two minutes every six weeks (4.8 mL).

Selected KEYTRUDA QLEX (pembrolizumab and berahyaluronidase alfa-pmph) Indications

Melanoma

KEYTRUDA QLEX is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

KEYTRUDA QLEX is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with Stage IIB, IIC, or III melanoma following complete resection.

Non-Small Cell Lung Cancer

KEYTRUDA QLEX, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA QLEX, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of adult patients with metastatic squamous NSCLC.

KEYTRUDA QLEX, as a single agent, is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:

- Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA QLEX.

KEYTRUDA QLEX is indicated for the treatment of adult patients with resectable (tumors ≥4 cm or node positive)

NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA QLEX, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

Malignant Pleural Mesothelioma

KEYTRUDA QLEX, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Squamous Cell Cancer

KEYTRUDA QLEX, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC.

KEYTRUDA QLEX, as a single agent, is indicated for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Urothelial Cancer

KEYTRUDA QLEX, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- who are not eligible for any platinum-containing chemotherapy, or
- who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

KEYTRUDA QLEX is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA QLEX is indicated for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

Gastric Cancer

KEYTRUDA QLEX, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

KEYTRUDA QLEX, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Esophageal Cancer

KEYTRUDA QLEX is indicated for the treatment of adult patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

KEYTRUDA QLEX, in combination with chemoradiotherapy (CRT), is indicated for the treatment of adult patients with FIGO 2014 Stage III-IVA cervical cancer.

KEYTRUDA QLEX, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Hepatocellular Carcinoma

KEYTRUDA QLEX is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

Biliary Tract Cancer

KEYTRUDA QLEX, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

Merkel Cell Carcinoma

KEYTRUDA QLEX is indicated for the treatment of adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal Cell Carcinoma

KEYTRUDA QLEX, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

KEYTRUDA QLEX is indicated for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

KEYTRUDA QLEX, in combination with carboplatin and paclitaxel, followed by KEYTRUDA QLEX as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA QLEX, as a single agent, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following

prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Cutaneous Squamous Cell Carcinoma

KEYTRUDA QLEX is indicated for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer

KEYTRUDA QLEX is indicated for the treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA QLEX, in combination with chemotherapy, is indicated for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Selected Important Safety Information for KEYTRUDA QLEX

Contraindications

KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients.

Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA QLEX is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti–PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For patients with TNBC treated with KEYTRUDA QLEX in the neoadjuvant setting, monitor blood cortisol

at baseline, prior to surgery, and as clinically indicated. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA QLEX depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA QLEX requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

KEYTRUDA QLEX can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 5% (13/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including fatal (0.4%), Grade 3 (2%), and Grade 2 (1.2%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving intravenous pembrolizumab, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of intravenous pembrolizumab in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Pneumonitis occurred in 7% (41/580) of adult patients with resected NSCLC who received intravenous pembrolizumab as a single agent for adjuvant treatment of NSCLC, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of intravenous pembrolizumab in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted intravenous pembrolizumab, 63% discontinued intravenous pembrolizumab, and 71% had resolution.

Immune-Mediated Colitis

KEYTRUDA QLEX can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In

cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.2% (3/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.8%) and Grade 2 (0.4%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of intravenous pembrolizumab in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA QLEX as a Single Agent

KEYTRUDA QLEX can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of intravenous pembrolizumab in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

KEYTRUDA QLEX With Axitinib

KEYTRUDA QLEX in combination with axitinib can cause hepatic toxicity. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider monitoring more frequently as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA QLEX and axitinib, and consider administering corticosteroids as needed.

With the combination of intravenous pembrolizumab and axitinib, Grades 3 and 4 increased alanine

aminotransferase (ALT) (20%) and increased aspartate aminotransferase (AST) (13%) were seen at a higher frequency compared to intravenous pembrolizumab alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either intravenous pembrolizumab (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving intravenous pembrolizumab, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA QLEX can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA QLEX depending on severity. Adrenal insufficiency occurred in 2% (5/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of intravenous pembrolizumab in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

Hypophysitis

KEYTRUDA QLEX can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity.

Intravenous Pembrolizumab as a Single Agent

Hypophysitis occurred in 0.6% (17/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent

discontinuation of intravenous pembrolizumab in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

Thyroid Disorders

KEYTRUDA QLEX can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity. Thyroiditis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%). Hyperthyroidism occurred in 8% (20/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (3.2%). Hypothyroidism occurred in 14% (35/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (11%).

Intravenous Pembrolizumab as a Single Agent

Thyroiditis occurred in 0.6% (16/2799) of patients receiving intravenous pembrolizumab, including Grade 2 (0.3%). None discontinued, but intravenous pembrolizumab was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of intravenous pembrolizumab in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of intravenous pembrolizumab in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving intravenous pembrolizumab as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving intravenous pembrolizumab as a single agent as adjuvant treatment, including Grade 3 (0.2%) hyperthyroidism. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving intravenous pembrolizumab as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) hypothyroidism.

Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as

clinically indicated. Withhold KEYTRUDA QLEX depending on severity. Type 1 diabetes mellitus occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy.

Intravenous Pembrolizumab as a Single Agent

Type 1 DM occurred in 0.2% (6/2799) of patients receiving intravenous pembrolizumab. It led to permanent discontinuation in <0.1% (1) and withholding of intravenous pembrolizumab in <0.1% (1) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement.

Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA QLEX can cause immune-mediated nephritis.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving intravenous pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to permanent discontinuation of intravenous pembrolizumab in 0.1% (3) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA QLEX can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti–PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA QLEX depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.6% (4/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 4 (0.8%) and Grade 3 (0.8%) adverse reactions.

Intravenous Pembrolizumab as a Single Agent

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving intravenous pembrolizumab, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of intravenous pembrolizumab in 0.6% (16) of patients. All patients who were withheld reinitiated intravenous pembrolizumab after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38

patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA QLEX, intravenous pembrolizumab, or were reported with the use of other anti–PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. Cardiac/Vascular: Myocarditis, pericarditis, vasculitis; Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis (2.8%), duodenitis; Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; Endocrine: Hypoparathyroidism; Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Hypersensitivity and Administration-Related Reactions

KEYTRUDA QLEX can cause severe or life-threatening administration-related reactions, including hypersensitivity and anaphylaxis. In Study MK-3475A-D77, hypersensitivity and administration-related systemic reactions occurred in 3.2% (8/251) of patients receiving KEYTRUDA QLEX, including Grade 2 (2.8%). Monitor patients for signs and symptoms of administration-related systemic reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt injection (if not already fully administered) and resume if symptoms resolve for mild or moderate hypersensitivity and administration-related systemic reactions. For severe or life-threatening hypersensitivity and administration-related systemic reactions, stop injection and permanently discontinue KEYTRUDA QLEX.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti–PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring

febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatments and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

Increased Mortality in Patients With Multiple Myeloma

In trials in patients with multiple myeloma, the addition of intravenous pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with an anti–PD-1/PD-L1 treatment in this combination is not recommended outside of controlled trials.

Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA QLEX can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA QLEX and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

In Study MK-3475A-D77, when KEYTRUDA QLEX was administered with chemotherapy in metastatic non-small cell lung cancer (NSCLC), serious adverse reactions occurred in 39% of patients. Serious adverse reactions in ≥1% of patients who received KEYTRUDA QLEX were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients including pneumonia (3.2%), febrile neutropenia (1.2%), respiratory failure (1.2%), neutropenic sepsis (0.4%), septic shock (0.4%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%). KEYTRUDA QLEX was permanently discontinued due to an adverse reaction in 16% of patients. Adverse reactions which resulted in permanent discontinuation of KEYTRUDA QLEX in ≥2% of patients included pneumonia and pneumonitis. Dosage interruptions of KEYTRUDA QLEX due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia, anemia, thrombocytopenia, pneumonia, rash, and increased aspartate aminotransferase. The most common adverse reactions (≥20%) were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).

In KEYNOTE-006, intravenous pembrolizumab was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). The

most common adverse reactions (≥20%) with intravenous pembrolizumab were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, when intravenous pembrolizumab was administered as a single agent to patients with stage III melanoma, intravenous pembrolizumab was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 25% of patients receiving intravenous pembrolizumab. The most common adverse reaction (≥20%) with intravenous pembrolizumab was diarrhea (28%). In KEYNOTE-716, when intravenous pembrolizumab was administered as a single agent to patients with stage IIB or IIC melanoma, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in 1011 patients with stage III melanoma from KEYNOTE-054.

In KEYNOTE-189, when intravenous pembrolizumab was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, intravenous pembrolizumab was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with intravenous pembrolizumab were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).

In KEYNOTE-407, when intravenous pembrolizumab was administered with carboplatin and either paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, intravenous pembrolizumab was discontinued due to adverse reactions in 15% of 101 patients. The most frequent serious adverse reactions reported in at least 2% of patients were febrile neutropenia, pneumonia, and urinary tract infection. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs 36%) and peripheral neuropathy (31% vs 25%) were observed in the intravenous pembrolizumab and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

In KEYNOTE-042, intravenous pembrolizumab was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), death due to unknown cause (1.6%), and pneumonia (1.4%). The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-010, intravenous pembrolizumab monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC; the most common was pneumonitis (1.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-671, adverse reactions occurring in patients with resectable NSCLC receiving intravenous pembrolizumab in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as single-agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving intravenous pembrolizumab in combination with chemotherapy.

The most common adverse reactions (reported in ≥20%) in patients receiving intravenous pembrolizumab in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism.

In the neoadjuvant phase of KEYNOTE-671, when intravenous pembrolizumab was administered in combination with platinum-containing chemotherapy as neoadjuvant treatment, serious adverse reactions occurred in 34% of 396 patients. The most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%). Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received intravenous pembrolizumab in combination with platinum-containing chemotherapy; the most frequent adverse reactions (≥1%) that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the intravenous pembrolizumab-treated patients who received neoadjuvant treatment, 6% of 396 patients did not receive surgery due to adverse reactions. The most frequent (≥1%) adverse reaction that led to cancellation of surgery in the intravenous pembrolizumab arm was interstitial lung disease (1%).

In the adjuvant phase of KEYNOTE-671, when intravenous pembrolizumab was administered as a single agent as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of intravenous pembrolizumab due to an adverse reaction occurred in 12% of patients who received intravenous pembrolizumab as a single agent, given as adjuvant treatment; the most frequent adverse reactions (≥1%) that led to permanent discontinuation of intravenous pembrolizumab were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and musculoskeletal pain (1%).

Adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving intravenous pembrolizumab as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

Adverse reactions observed in KEYNOTE-483 were generally similar to those occurring in other patients receiving intravenous pembrolizumab in combination with pemetrexed and platinum chemotherapy.

In KEYNOTE-048, intravenous pembrolizumab monotherapy was discontinued due to adverse events in 12% of 300 patients with HNSCC; the most common adverse reactions leading to permanent discontinuation were sepsis (1.7%) and pneumonia (1.3%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when intravenous pembrolizumab was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, intravenous pembrolizumab was discontinued due to adverse reactions in 16% of 276 patients with HNSCC. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (26%), and cough (22%).

In KEYNOTE-012, intravenous pembrolizumab was discontinued due to adverse reactions in 17% of 192 patients with HNSCC. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (≥20%) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a monotherapy, with the exception of increased incidences of facial edema and new or worsening hypothyroidism.

In KEYNOTE-A39, when intravenous pembrolizumab was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer (n=440), fatal adverse reactions occurred in 3.9% of patients, including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%). Serious adverse reactions occurred in 50% of patients receiving intravenous pembrolizumab in combination with enfortumab vedotin; the serious adverse reactions in ≥2% of patients were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%). Permanent discontinuation of intravenous pembrolizumab occurred in 27% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of intravenous pembrolizumab were pneumonitis/ILD (4.8%) and rash (3.4%). The most common adverse reactions (≥20%) occurring in patients treated with intravenous pembrolizumab in combination with enfortumab vedotin were rash (68%), peripheral neuropathy (67%), fatigue (51%), pruritus (41%), diarrhea (38%), alopecia (35%), weight loss (33%), decreased appetite (33%), nausea (26%), constipation (26%), dry eye (24%), dysgeusia (21%), and urinary tract infection (21%).

In KEYNOTE-052, intravenous pembrolizumab was discontinued due to adverse reactions in 11% of 370 patients

with locally advanced or metastatic urothelial carcinoma. Serious adverse reactions occurred in 42% of patients; those ≥2% were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%).

In KEYNOTE-045, intravenous pembrolizumab was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab was pneumonitis (1.9%). Serious adverse reactions occurred in 39% of intravenous pembrolizumab-treated patients; those ≥2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received intravenous pembrolizumab were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite (21%), nausea (21%), and rash (20%).

In KEYNOTE-057, intravenous pembrolizumab was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab was pneumonitis (1.4%). Serious adverse reactions occurred in 28% of patients; those ≥2% were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (29%), diarrhea (24%), and rash (24%).

Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a monotherapy.

In KEYNOTE-158 and KEYNOTE-164, adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received intravenous pembrolizumab as a single agent.

In KEYNOTE-811, when intravenous pembrolizumab was administered in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, intravenous pembrolizumab was discontinued due to adverse reactions in 6% of 217 patients with locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma. The most common adverse reaction resulting in permanent discontinuation was pneumonitis (1.4%). In the intravenous pembrolizumab arm vs placebo, there was a difference of ≥5% incidence between patients treated with intravenous pembrolizumab vs standard of care for diarrhea (53% vs 44%) and nausea (49% vs 44%).

In KEYNOTE-859, when intravenous pembrolizumab was administered in combination with fluoropyrimidine- and platinum-containing chemotherapy, serious adverse reactions occurred in 45% of 785 patients. Serious adverse reactions in >2% of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%).

Fatal adverse reactions occurred in 8% of patients who received intravenous pembrolizumab, including infection (2.3%) and thromboembolism (1.3%). Intravenous pembrolizumab was permanently discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) were infections (1.8%) and diarrhea (1.0%). The most common adverse reactions (reported in ≥20%) in patients receiving intravenous pembrolizumab in combination with chemotherapy were peripheral neuropathy (47%), nausea (46%), fatigue (40%), diarrhea (36%), vomiting (34%), decreased appetite (29%), abdominal pain (26%), palmar-plantar erythrodysesthesia syndrome (25%), constipation (22%), and weight loss (20%).

In KEYNOTE-590, when intravenous pembrolizumab was administered with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation, intravenous pembrolizumab was discontinued due to adverse reactions in 15% of 370 patients. The most common adverse reactions resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). The most common adverse reactions (≥20%) with intravenous pembrolizumab in combination with chemotherapy were nausea (67%), fatigue (57%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

Adverse reactions occurring in patients with esophageal cancer who received intravenous pembrolizumab as a monotherapy were similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a monotherapy.

In KEYNOTE-A18, when intravenous pembrolizumab was administered with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) to patients with FIGO 2014 Stage III-IVA cervical cancer, fatal adverse reactions occurred in 1.4% of 292 patients, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage. Serious adverse reactions occurred in 30% of patients; those ≥1% included urinary tract infection (2.7%), urosepsis (1.4%), and sepsis (1%). Intravenous pembrolizumab was discontinued for adverse reactions in 7% of patients. The most common adverse reaction (≥1%) resulting in permanent discontinuation was diarrhea (1%). For patients treated with intravenous pembrolizumab in combination with CRT, the most common adverse reactions (≥10%) were nausea (56%), diarrhea (50%), vomiting (33%), urinary tract infection (32%), fatigue (26%), hypothyroidism (20%), constipation (18%), decreased appetite and weight loss (17% each), abdominal pain and pyrexia (12% each), hyperthyroidism, dysuria, rash (11% each), and pelvic pain (10%).

In KEYNOTE-826, when intravenous pembrolizumab was administered in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab (n=307), to patients with persistent, recurrent, or first-

line metastatic cervical cancer regardless of tumor PD-L1 expression who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent, fatal adverse reactions occurred in 4.6% of patients, including 3 cases of hemorrhage, 2 cases each of sepsis and due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection. Serious adverse reactions occurred in 50% of patients receiving intravenous pembrolizumab in combination with chemotherapy with or without bevacizumab; those ≥3% were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury and sepsis (3.3% each).

Intravenous pembrolizumab was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation (≥1%) was colitis (1%).

For patients treated with intravenous pembrolizumab, chemotherapy, and bevacizumab (n=196), the most common adverse reactions (≥20%) were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea and neutropenia (41% each), diarrhea (39%), hypertension and thrombocytopenia (35% each), constipation and arthralgia (31% each), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

For patients treated with intravenous pembrolizumab in combination with chemotherapy with or without bevacizumab, the most common adverse reactions (≥20%) were peripheral neuropathy (58%), alopecia (56%), fatigue (47%), nausea (40%), diarrhea (36%), constipation (28%), arthralgia (27%), vomiting (26%), hypertension and urinary tract infection (24% each), and rash (22%).

In KEYNOTE-158, intravenous pembrolizumab was discontinued due to adverse reactions in 8% of 98 patients with previously treated recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving intravenous pembrolizumab; the most frequent included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).

In KEYNOTE-394, intravenous pembrolizumab was discontinued due to adverse reactions in 13% of 299 patients with previously treated hepatocellular carcinoma. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab was ascites (2.3%). The most common adverse reactions in patients receiving intravenous pembrolizumab (≥10%) were pyrexia (18%), rash (18%), diarrhea (16%), decreased appetite (15%), pruritus (12%), upper respiratory tract infection (11%), cough (11%), and hypothyroidism (10%).

In KEYNOTE-966, when intravenous pembrolizumab was administered in combination with gemcitabine and cisplatin, intravenous pembrolizumab was discontinued for adverse reactions in 15% of 529 patients with locally

advanced unresectable or metastatic biliary tract cancer. The most common adverse reaction resulting in permanent discontinuation of intravenous pembrolizumab (≥1%) was pneumonitis (1.3%). Adverse reactions leading to the interruption of intravenous pembrolizumab occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of intravenous pembrolizumab (≥2%) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood cell count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In KEYNOTE-017 and KEYNOTE-913, adverse reactions occurring in patients with MCC (n=105) were generally similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a single agent.

In KEYNOTE-426, when intravenous pembrolizumab was administered in combination with axitinib, fatal adverse reactions occurred in 3.3% of 429 patients. Serious adverse reactions occurred in 40% of patients, the most frequent (≥1%) were hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%). Permanent discontinuation due to an adverse reaction occurred in 31% of patients; intravenous pembrolizumab only (13%), axitinib only (13%), and the combination (8%); the most common were hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). The most common adverse reactions (≥20%) were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), nausea (28%), stomatitis/mucosal inflammation (27%), dysphonia (25%), rash (25%), cough (21%), and constipation (21%).

In KEYNOTE-564, when intravenous pembrolizumab was administered as a single agent for the adjuvant treatment of renal cell carcinoma, serious adverse reactions occurred in 20% of patients receiving intravenous pembrolizumab; the serious adverse reactions (≥1%) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% including 1 case of pneumonia. Discontinuation of intravenous pembrolizumab due to adverse reactions occurred in 21% of 488 patients; the most common (≥1%) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%). The most common adverse reactions (≥20%) were musculoskeletal pain (41%), fatigue (40%), rash (30%), diarrhea (27%), pruritus (23%), and hypothyroidism (21%).

In KEYNOTE-868, when intravenous pembrolizumab was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma (n=382), serious adverse reactions occurred in 35% of patients receiving intravenous pembrolizumab in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy (n=377). Fatal adverse reactions occurred in 1.6% of patients receiving intravenous pembrolizumab in combination with chemotherapy, including COVID-19 (0.5%) and cardiac arrest (0.3%). Intravenous pembrolizumab was discontinued for an adverse reaction in

14% of patients. Adverse reactions occurring in patients treated with intravenous pembrolizumab and chemotherapy were generally similar to those observed with intravenous pembrolizumab alone or chemotherapy alone, with the exception of rash (33% all Grades; 2.9% Grades 3-4).

Adverse reactions occurring in patients with MSI-H or dMMR endometrial carcinoma who received intravenous pembrolizumab as a single agent were similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a single agent.

Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in patients with melanoma or NSCLC who received intravenous pembrolizumab as a monotherapy.

In KEYNOTE-522, when intravenous pembrolizumab was administered with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with intravenous pembrolizumab as a single agent (n=778) to patients with newly diagnosed, previously untreated, high-risk early-stage TNBC, fatal adverse reactions occurred in 0.9% of patients, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving intravenous pembrolizumab; those ≥2% were febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). Intravenous pembrolizumab was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (2.7%), increased AST (1.5%), and rash (1%). The most common adverse reactions (≥20%) in patients receiving intravenous pembrolizumab were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

In KEYNOTE-355, when intravenous pembrolizumab and chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) were administered to patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting (n=596), fatal adverse reactions occurred in 2.5% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.3%). Serious adverse reactions occurred in 30% of patients receiving intravenous pembrolizumab in combination with chemotherapy; the serious reactions in ≥2% were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). Intravenous pembrolizumab was discontinued in 11% of patients due to adverse reactions. The most common reactions resulting in permanent discontinuation (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) in patients receiving intravenous pembrolizumab in combination with chemotherapy were fatigue (48%), nausea (44%), alopecia (34%), diarrhea and constipation (28%

each), vomiting and rash (26% each), cough (23%), decreased appetite (21%), and headache (20%).

Lactation

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the last dose.

Pediatric Use

In KEYNOTE-051, 173 pediatric patients (including 108 pediatric patients aged 12 years to 17 years) were administered intravenous pembrolizumab 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 25 months).

The safety and effectiveness of KEYTRUDA QLEX for the treatment of pediatric patients 12 years and older who weigh greater than 40 kg have been established for:

- Stage IIB, IIC, or III melanoma following complete resection
- Unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
- Recurrent locally advanced or metastatic Merkel cell carcinoma

Use of KEYTRUDA QLEX in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies of intravenous pembrolizumab in adults and additional pharmacokinetic and safety data for intravenous pembrolizumab in pediatric patients 12 years and older. Pembrolizumab exposures in pediatric patients 12 years and older who weigh greater than 40 kg are predicted to be within range of those observed in adults at the same dosage.

The safety and effectiveness of KEYTRUDA QLEX have not been established in pediatric patients younger than 12 years of age for the treatment of melanoma, MCC, MSI-H or dMMR cancer.

The safety and effectiveness of KEYTRUDA QLEX have not been established in pediatric patients for other approved indications shown.

Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (33%), leukopenia (30%), vomiting (29%), neutropenia (28%), headache (25%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

Geriatric Use

Of the 564 patients with locally advanced or metastatic urothelial cancer treated with intravenous pembrolizumab in combination with enfortumab vedotin, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with intravenous pembrolizumab in combination with enfortumab vedotin experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

About Merck

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Forward-Looking Statement of Merck & Co., Inc., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for

innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2024 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (**www.sec.gov**).

Please see Prescribing Information for KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) at **https://www.merck.com/product/usa/pi_circulars/k/keytruda_qlex/keytruda_qlex_pi.pdf** and Medication Guide for KEYTRUDA QLEX™ at **https://www.merck.com/product/usa/pi_circulars/k/keytruda_qlex/keytruda_qlex_mg.pdf**.

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